REMARKS

Claims 35-58 have been added. Support for new claims 35, 41, 47, and 53 is found, for example, on page 13, line 32 – page 14, line 28 of the specification as filed. Support for new claims 36-37, 42-43, 48-49, and 54-55 is found, for example, on page 8, lines 2-10 and in original claims 19-20 of the specification as filed. Support for new claims 38, 44, 50, and 56 is found, for example, on page 10, lines 1-2 of the specification as filed. Support for new claims 39, 45, 51, and 57 is found, for example, on page 11, lines 28-31 of the specification as filed. Support for new claims 40, 46, 52, and 58 is found, for example, on page 15, lines 2-6 and on page 16, lines 10-14 of the specification as filed.

(1) Pending Claim Rejections under 35 U.S.C. § 102 over Abraham et al.

(a) Rejection of claims 4-6

The Examiner has rejected claims 4-6 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,993,844 to Abraham et al. (the '844 patent). The Examiner indicates that the '844 patent anticipates claims 4-6 because the '844 patent describes graft constructs that are endotoxin-free and, according to the Examiner, a graft construct that is "endotoxin-free" is within the ranges claimed in the present application. Furthermore, the Examiner asserts that the effective filing date of claims 4-6, 9, 10, and 16-20 is August 22, 1997 because, according to the Examiner, support for the range of "an endotoxin level of less than 12 endotoxin units per gram" is not present in the provisional applications from which the instant application claims priority. Applicants respectfully traverse the Examiner's rejection.

Claims 4-6 are not anticipated by the '844 patent because the prior art does not set forth each and every element of the claims. Anticipation exists only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art

reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In the instant rejection, the '844 patent does not describe grafts comprising a purified, collagen-based matrix structure with a bioburden level defined by colony forming units per gram. The '844 patent describes a chemical cleaning method that renders biologic material "substantially acellular and substantially free of non-collagenous components." (see column 4, lines 49-53 of the '844 patent). The phrase "substantially free of non-collagenous components" is defined in the '844 patent as amounts of glycoproteins, glycosaminoglycans, proteoglycans, lipids, non-collagenous proteins and nucleic acids, such as DNA and RNA, that "comprise less than 5% of the resultant tissue matrix." (see column 4, lines 61-66 of the '844 patent). However, the '844 patent does not quantify the purification of tissue in terms of colony forming units. In fact, the term "colony forming unit" is ***completely absent*** from the '844 patent.

In contrast, claims 4-6 of the present application describe graft prostheses with a bioburden level defined in terms of colony forming units. Accordingly, the '844 patent does not describe each and every element as set forth in the claims. Withdrawal of the rejection of claims 4-6 under 35 U.S.C. § 102(e) as being anticipated by the '844 patent is respectfully requested.

(b) Rejection of claims 9-10 and 16-20

The Examiner has rejected claims 9-10 and 16-20 under 35 U.S.C. § 102(e) as allegedly being anticipated by the '844 patent or, in the alternative, as being obvious under 35 U.S.C. § 103(a) over the '844 patent. Applicants respectfully traverse the Examiner's rejection of claims 9-10 and 16-20.

Anticipation exists only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Claims 9-10 and 16-20 are not anticipated by the '844 patent because the prior art does not set forth each and every element of the Applicants' claims.

Independent claims 9, 10, and 16 are directed to a graft prosthesis comprising a purified, collagen-based matrix structure wherein the submucosa tissue source is cleaned or treated to remove contaminants ***before*** the submucosa tissue source is delaminated. Importantly, the '844 patent does not describe cleaning of the submucosa tissue prior to delamination. In contrast, the '844 patent requires delamination of submucosa tissue prior to any cleaning of the tissue (see Example 1, found at column 11, line 34 to column 12, line 24 of the '844 patent). Accordingly, the '844 patent does not describe each and every element as set forth in claims 9-10 and 16-20.

Second, the Examiner has concluded that claims 9-10 and 16-20 are product-by-process claims. According to MPEP § 2113, "[t]he structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the ***manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.***" MPEP § 2113 (quoting *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979) (emphasis added).

If pending claims 9-10 and 16-20 are product-by-process claims (as indicated by the Examiner), the process steps impart the requisite distinctive structural characteristics to the final product. Claims 9-10 and 16-20 are each directed to a purified collagen-based matrix structure. As stated previously, the process steps in the claims describe preparation of the matrix structure wherein the submucosa tissue is cleaned or treated to remove contaminants ***before*** the submucosa tissue is delaminated. Importantly, these process steps impart distinctive characteristics to the final purified product. In Examples 4 and 5 of the specification as filed, a purified product prepared according to the method described in claims 9-10 and 16-20 (i.e., wherein the submucosa tissue is cleaned or treated to remove contaminants ***before*** the submucosa tissue is delaminated) was shown to have lower endotoxin levels compared to a product prepared

according to methods where submucosa tissue was cleaned ***after*** the tissue was delaminated (see page 22, line 22 to page 23, line 17 of the specification as filed). Therefore, the process steps described in claims 9-10 and 16-20 impart distinctive structural characteristics (e.g., lower endotoxin levels) to the final product and the matrix structure implied by the process steps of the claims should be considered when assessing the patentability of the claims over the prior art.

In contrast to the process steps of claims 9-10 and 16-20, the methods in the '844 patent describe a matrix of submucosa tissue that was cleaned ***after*** the tissue was delaminated. Thus, the matrix prepared according to the '844 patent has different structural characteristics than the matrix prepared according to Applicants' claims 9-10 and 16-20. Accordingly, if pending claims 9-10 and 16-20 are product-by-process claims as indicated by the Examiner, the claims are not anticipated by the '844 patent. Withdrawal of the rejection of claims 9-10 and 16-20 under 35 U.S.C. § 102(e) as being anticipated by the '844 patent is respectfully requested.

(b) Claims 1 and 11

Applicants note that the Examiner acknowledges that claims 1 and 11 have an effective filing date of August 23, 1996, which is prior to the effective date of the '844 patent.

(2) Pending Claim Rejections under 35 U.S.C. § 103 over Abraham et al.

The Examiner has rejected claims 9-10 and 16-20, in the alternative, as being obvious under 35 U.S.C. § 103(a) over the '844 patent. Applicants respectfully traverse the Examiner's rejection of claims 9-10 and 16-20.

First, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Therefore, in order for Applicants' invention to be rendered obvious under 35 U.S.C. § 103, the combination of references relied upon by the Examiner must teach each and every element of Applicants' invention, as defined by claims 9-10 and 16-20.

The '844 patent does not teach or suggest cleaning of the submucosa tissue prior to delamination. Instead, the '844 patent requires delamination of submucosa tissue prior to any cleaning of the tissue (see Example 1, found at column 11, line 34 – column 12, line 24 of the '844 patent). Claims 9-10 and 16-20 describe a submucosa tissue that is cleaned ***prior*** to being delaminated. The '844 patent provides no suggestion of the claimed method. Accordingly, claims 9-10 and 16-20 are not obvious over the '844 patent. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness and the rejection of claims 9-10 and 16-20 under 35 U.S.C. § 103 is improper. Withdrawal of the rejection of claims 9-10 and 16-20 under 35 U.S.C. § 103(a) over the '844 patent is respectfully requested.

Second, the Examiner has concluded that claims 9-10 and 16-20 are product-by-process claims. According to MPEP § 2113, "[t]he structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the ***manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.***" MPEP § 2113 (quoting *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979) (emphasis added).

If pending claims 9-10 and 16-20 are product-by-process claims (as indicated by the Examiner), the process steps impart the requisite distinctive structural characteristics to the final product. Claims 9-10 and 16-20 are each directed to a purified collagen-based matrix structure. As stated previously, the process steps in the claims describe preparation of the matrix structure wherein the submucosa tissue is cleaned or treated to remove contaminants ***before*** the submucosa tissue is delaminated. Importantly, these process steps impart distinctive characteristics to the final purified product. In Examples 4 and 5 of the specification as filed, a purified product prepared according to the method described in claims 9-10 and 16-20 (i.e., wherein the submucosa tissue is cleaned or treated to remove contaminants ***before*** the submucosa

tissue is delaminated) was shown to have lower endotoxin levels compared to a product prepared according to methods where submucosa tissue was cleaned ***after*** the tissue was delaminated (see page 22, line 22 to page 23, line 17 of the specification as filed). Therefore, the process steps described in claims 9-10 and 16-20 impart distinctive structural characteristics (e.g., lower endotoxin levels) to the final product and the matrix structure implied by the process steps of the claims should be considered when assessing the patentability of the claims over the prior art.

In contrast to the process steps of claims 9-10 and 16-20, the methods in the '844 patent describe a matrix of submucosa tissue that was cleaned ***after*** the tissue was delaminated. Thus, the matrix prepared according to the '844 patent has different structural characteristics than the matrix prepared according to Applicants' claims 9-10 and 16-20. Accordingly, if pending claims 9-10 and 16-20 are product-by-process claims as indicated by the Examiner, the claims are not anticipated by the '844 patent. Withdrawal of the rejection of claims 9-10 and 16-20 under 35 U.S.C. § 102(e) as being anticipated by the '844 patent is respectfully requested.

(3) Pending Claim Rejections under 35 U.S.C. § 102 and 35 U.S.C. § 103 over Yannas et al.

Applicants respectfully point out that claim 14 in the application has been canceled. Accordingly, Applicants assume that the Examiner has rejected independent claims 1 and 11, rather than claims 1 and 14, in the present rejections under 35 U.S.C. § 102 and 35 U.S.C. § 103 over Yannas et al. (hereinafter "the '081 patent"). The following discussion is based on this assumption.

The Examiner asserts that the '081 patent anticipates claims 1 and 11 where purified collagen is used to make the graft because it is "indistinguishable from collagen of other sources in that all the other source components have been removed." Furthermore, the Examiner contends that the purified structure described in the '081 patent is inherently free of endotoxins because all endotoxins have been removed. Applicants respectfully traverse the Examiner's

rejection. Claims 1 and 11 are not anticipated by the '081 patent and, moreover, are not obvious over the '081 patent.

(a) Collagen Structure in the '081 Patent is not Inherently Free of Endotoxins

The Examiner has not met his burden of proof to establish that the "purified" collagen structure in the '081 patent is inherently free of endotoxins. According to the Manual of Patent Examining Procedure, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic ***necessarily*** flows from the teachings of the applied prior art." MPEP § 2112(IV) (quoting *Ex Parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)) (emphasis original). In the present rejection, the Examiner simply states that the "purified" collagen structure in the '081 patent is inherently free of endotoxins because all endotoxins have been removed via the process of purification.

According to the Manual of Patent Examining Procedure, "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP § 2112(IV) (emphasis original). In the present Office Action, the Examiner has simply stated that the collagen structure described in the '081 patent "is inherently free of endotoxins because all endotoxins have been removed." Accordingly, the Examiner has not met his burden to prove that the "purified" collagen structure in the '081 patent is inherently free of endotoxins. Furthermore, according to MPEP § 2141.02(V), "[o]bviousness cannot be predicted on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). Claims 1 and 11 of the present application are not anticipated by the '081 patent and are not obvious over the teachings of the '081 patent. Withdrawal of the rejection of claims 1 and 11 under 35 U.S.C. § 102(b) and under 35 U.S.C. § 103(a) in view of the '081 patent is respectfully requested.

(4) New Claims 35-58 are Novel and Unobvious over the '081 Patent

New independent claims 35 and 41 are directed to the graft prosthesis embodiment as claimed in pending claims 1 and 11, respectively, and specify that the structure further comprises a component selected from the group consisting of glycoproteins, glycosaminoglycans, and proteoglycans. New independent claims 47 and 53 are directed to the graft prosthesis embodiment as claimed in pending claims 1 and 11, respectively, and specify that the structure further comprises a growth factor. New claims 35-58 are novel and unobvious over the '081 patent.

On page 4, third full paragraph of the present Office Action, the Examiner states that "[the '081 patent] anticipates the claim language where purified collagen is used to make the graft so it is indistinguishable from collagen of other sources in that ***all the other source components have been removed.***" (emphasis added). The Examiner goes on to state that the structure described by the '081 patent "is inherently free of endotoxins because ***all endotoxins have been removed by the process of purification.***" (emphasis added). Therefore, according to the Examiner, the '081 patent teaches that the structure described in the '081 patent is purified to remove all source components other than collagen.

Anticipation exists only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The '081 patent does not teach a collagen-based matrix structure that further comprises a component such as a glycoprotein, a glycosaminoglycan, a proteoglycan, or a growth factor. In contrast, new claims 35-58 specify that the claimed structure further comprises a component selected from the group consisting of glycoproteins, glycosaminoglycans, and proteoglycans or a growth factor. Therefore, new claims 35-58 are not anticipated by the '081 patent.

Furthermore, new claims 35-58 are unobvious over the '081 patent. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *See* MPEP § 2141; *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). The '081 patent teaches away from new claims 35, 41, 47, and 53 and their dependent claims.

The '081 patent (as stated by the Examiner on page 4, third full paragraph of the present Office Action) describes a collagen structure in which ***all the other source components have been removed.***" (emphasis added). Therefore, according to the Examiner, the '081 patent teaches that all components other than collagen must be removed from the structure. In contrast, new claims 35-58 specify that the claimed structure further comprises a component selected from the group consisting of glycoproteins, glycosaminoglycans, and proteoglycans or a growth factor. Therefore, new claims 35-58 include a component other than collagen, contrary to the Examiner's stated teachings of the '081 patent.

Thus, the '081 patent teaches away from Applicants' invention as defined by new claims 35-58. According to the Examiner, the structure described in the '081 patent is a collagen structure with all other source components removed. This structure cannot render obvious a composition that further includes a component selected from the group consisting of glycoproteins, glycosaminoglycans, and proteoglycans or a growth factor. Accordingly, Applicants' new claims 35-58 are not obvious over the '081 patent.

CONCLUSION

The foregoing amendments and remarks are believed to fully respond to the Examiner's rejections. Applicants respectfully request issuance of an action indicating that the claims are allowable, and issuance of a declaration of interference.

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